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APPLICATION OF MAGNESIUM DRUGS AND THEIR INFLUENCE ON THE INDICATORS OF CONNECTIVE TISSUE DYSPLASIA IN PATIENTS WITH VARICOSE VEINS

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Цель. Изучение влияния приема препаратов магния на концентрацию матричных металлопротеиназ и ионов магния у пациентов с варикозной болезнью вен нижних конечностей.

Материал и методы. В исследование включено 124 пациента с варикозной болезнью вен нижних конечностей (ВБВНК) классов C2-C6, которых разделили на 4 группы. В I-й группе проводили оперативное лечение с последующим назначением стандартного консервативного лечения (32 человека); во II-й группе после операции в дополнение к консервативному лечению назначали препараты магния (32 человека); в III-й группе проводили консервативное лечение без операции (30 человек); в IV-й группе пациенты получали стандартное консервативное лечение и препараты магния (30 человек). V-ю контрольную группу составили 20 здоровых добровольцев, не страдающих варикозной болезнью. Пациентам II-й и IV-й групп назначали магния оротат 500 мг 2 табл. 3 раза в день в течение 3 мес. Содержание в сыворотке крови матричной металлопротеиназы-1 (ММП-1), матричной металлопротеиназы-9 (ММП-9), тканевого ингибитора матричной металлопротеиназы-1 (ТИМП-1) определяли методом количественного твердофазного иммуноферментного анализа. Концентрацию ионов магния определяли колориметрическим методом.

Результаты. У пациентов с ВБВНК отмечался достоверно меньший уровень магния по сравнению с условно здоровыми добровольцами, не страдающими варикозной болезнью: 35,5% среди страдающих варикозной болезнью имели дефицит магния, в то время как всего 15% имели снижение данного показателя среди здоровых добровольцев. На фоне проводимой дополнительной терапии препаратами магния, отмечалось уменьшение количества пациентов с дефицитом магния в группах с ВБВНК, снижение концентрации ММП-9 и повышение активности ТИМП-1.

Заключение. Исследование подтвердило эффективность применения препаратов магния, которые обладают выраженным влиянием на процессы деградации коллагена и внеклеточного матрикса, снижают активность ММП-9, повышают концентрацию ТИМП-1, тем самым влияя на баланс ММП/ТИМП у пациентов с ВБВНК.

Ключевые слова: первичное варикозное расширение вен, фармакотерапия, магний, матричные металлопротеиназы, дисплазия соединительной ткани

Objective. To study the effect of magnesium drugs on the concentration of matrix metalloproteinases and magnesium ions in patients with varicose veins of the lower extremities.

Methods. The study included 124 patients with varicose veins of the lower extremities, C2-C6, which were divided into 4 groups. In the 1st group, surgical treatment followed with the administering the standard conservative treatment (32 patient); in the 2nd group after the operation in addition to conservative treatment, magnesium drugs (32 patient) were prescribed; in the 3rd group, conservative treatment without surgery (30 patient) was performed; in the 4th group patients received standard conservative treatment and magnesium drugs (30 patient). The 5th control group consisted of 20 healthy volunteers who did not suffer from varicose veins disease. Patients of groups 2 and 4 were given magnesium orotate 500 mg 2 tablets 3 times a day for 3 months. The content of serum matrix metalloproteinase-1 (MMP-1), matrix metalloproteinase-9 (MMP-9), tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) was determined by quantitative solid-phase enzyme immunoassay. The magnesium ion concentration was determined by colorimetric method.

Results. In patients with varicose veins of lower extremities a significantly lower level of magnesium was registered compared to healthy volunteers not suffering from varicose veins: 35.5% of those with varicose veins had a magnesium deficiency, while only 15% had a decrease in this indicator among healthy volunteers. Against the background of additional therapy with magnesium drugs, there was a decrease in the number of patients with magnesium deficiency in groups with varicose veins of lower extremities, a decrease in MMP-9 concentration and an increase in TIMP-1 activity was also established.

Conclusions. This study has confirmed the efficacy of magnesium drugs which have a pronounced effect on collagen degradation processes and extracellular matrix, reduce the activity of MMP-9, increase the concentration of TIMP-1, thereby affecting the MMP/TIMP balance in patients with varicose veins of lower extremities.

Keywords: primary varicose veins, pharmacotherapy, magnesium, matrix metalloproteinase, connective tissue dysplasia

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Application of Magnesium Drugs and Their Influence on the Indicators of Connective Tissue Dysplasia in Patients with Varicose Veins

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Научная новизна статьи

Произведена комплексная биохимическая оценка маркеров дисплазии соединительной ткани (ионов магния, матриксных металлопротеиназ, тканевого ингибитора матриксных металлопротеиназ) у пациентов с варикозной болезнью нижних конечностей. Проведен анализ влияния препаратов магния в лечении данной патологии. Подтверждена целесообразность применения препаратов магния у пациентов с варикозной болезнью, в том числе и у перенесших флебэктомию, с позиции влияния их на уровень матриксных металлопротеиназ и их ингибиторов.

What this paper adds

A complex biochemical assessment of markers of connective tissue dysplasia (magnesium ions, matrix metalloproteinases, tissue inhibitor of matrix metalloproteinases) in patients with varicose veins has been performed. An analysis of the effect of magnesium drugs in the treatment of this pathology has been conducted. The expediency of using magnesium drugs in patients with varicose veins, including those who underwent phlebectomy, has been confirmed from the position of their influence on the level of matrix metalloproteinases and their inhibitors.

Introduction

Varicose veins of the lower extremities are one of the most common diseases of peripheral vessels [1, 2, 3]. According to leading Russian phlebologists, more than 35 million people suffer from chronic venous insufficiency (CVI), which develops against the background of varicose veins, 15% of them have complicated forms of the disease [4].

Despite the successes achieved in the treatment and diagnosis of patients with varicose veins, many unsolved problems still remain, both theoretical and practical. We have to state that still much remains unclear in etiology and pathogenesis of varicose veins, which, in fact, is represented by a certain set of risk factors, the priority and significance of which may be different [5].

Several years ago, the idea about the participation of special matrix enzymes – metalloproteinases in the development of varicose veins of the subcutaneous veins was stated for the first time. Metalloproteinases play an important role in the development of such physiological processes as morphogenesis, resorption, tissue remodeling, angiogenesis. The function of metalloproteinases consists in the degradation of various protein components of the intercellular matrix (collagen, elastin, fibronectin, glycosaminoglycan) and, in general, in maintaining its homeostasis. In the preservation of metalloproteinases in a latent form and preventing their excessive activation, tissue inhibitors of metalloproteinases play an important role. Among them, the tissue inhibitor metalloproteinases-1 (TIMP-1) regulates the activity of matrix metalloproteinase-1 (MMP-1) and matrix metalloproteinase-9 (MMP-9) in the body. For the normal course of the processes of the extracellular matrix reorganization, it is

necessary to maintain an equilibrium between the activity of metalloproteinases and their inhibitors [6, 7].

Also, according to modern concepts, varicose veins are a group of hereditary diseases that are directly related to a violation of synthesis or degradation of fibrous connective tissue structures that occur in the embryonic and postnatal periods of life. Understanding the role of magnesium in maintaining the structure of connective tissue is inseparable from the molecular-cellular structure of connective tissue. Magnesium is a universal regulator of biochemical and physiological processes in the body: it participates in energy, plastic and electrolyte metabolism [8, 9]. Magnesium as a physiological factor in synthesis of collagen is of particular interest.

Experiments on animals confirm the effect of magnesium on the biological activity of MMP. In mice with artificially induced magnesium deficiency, there is a significant thinning of the aortic wall compared to control animals. The specific coloration of the two main types of fibers (collagen and elastin) has shown significant structural changes in both components. These changes correlated with an increase in the total activity of matrix metalloproteinases MMP-2 and MMP-9 [10].

The data given above suggest that the Mg^{2+} deficiency should probably lead to an increase in MMP activity, which begin to destroy the structural components of the extracellular matrix (ECM) (primarily collagen) at a higher rate, and also affect the tissue inhibitors of matrix metalloproteinases.

Objective. To study the effect of magnesium drugs on the concentration of matrix metalloproteinases and magnesium ions in patients with varicose veins of the lower extremities.

Methods

The study included 124 patients with varicose veins, C2-C6, which were divided into 4 groups. In the 1st group, surgical treatment followed with the administering the standard conservative treatment (32 patient); in the 2nd group after the operation in addition to conservative treatment, magnesium drugs (32 patient) were prescribed; in the 3rd group, conservative treatment without surgery (30 patient) was performed; in the 4th group patients received standard conservative treatment and magnesium drugs (30 patient). The 5th control group consisted of 20 healthy volunteers who did not suffer from varicose veins. Patients of groups 2 and 4 were given magnesium orotate 500 mg 2 tablets 3 times a day for 3 months. The study was not of an intervention nature, the choice of the treatment option was determined by the attending physician, taking into account the capabilities and desires of a patient.

The study was approved by the ethical committee of the Ryazan State Medical University named after Academician I.P. Pavlov.

The groups were comparable by sex, age, concomitant diseases, clinical class and duration of the disease. The distribution of patients by group, sex and age is presented in Table 1.

The criterion for inclusion in the study of patients of groups I-IV was clinically and instrumentally verified varicose veins of the lower extremities, in the control group – the absence of varicose veins. Exclusion criteria were previous thrombophlebitis of the superficial veins of the lower limbs; deep vein thrombosis of the lower limbs; obliterating diseases of the aorta, peripheral artery disease of the pelvis and lower limbs; coronary artery disease, acute impairment of cerebral circulation in the anamnesis; diabetes; operations and manipulations on the superficial veins of the lower limbs; infectious-inflammatory diseases of

soft tissues of the lower limbs. The study was approved by a local ethics committee and all patients signed the informed consent to participate in the study.

The samples of peripheral blood taken in the morning on an empty stomach were examined. The serum levels of MMP-9, MMP-1, and TIMP-1 were determined by quantitative solid-phase enzyme immunoassay method using enzyme immunoassay kit for quantitative in vitro detection of matrix metalloproteinases in serum, blood plasma and other biological fluids, as well as cell lysates and supernatant of cell cultures (AbFrontier human MMP-1 ELISA, China, Bender MedSystems human MMP-9 ELISA, USA; Bender MedSystems human TIMP-9 ELISA, USA).

The concentration of Mg^{2+} was determined by photolorimetric method using the "MAGNIUM-OLVEX" kit (Olvex-Diagnosticum, Russia). Blood sampling for determining the level of biochemical markers was carried out at the beginning of the study and subsequently 1, 3 and 6 months after the start of treatment in patients with conservative and operative groups with varicose veins.

Statistics

The determination of the mean values, the standard deviation and the error of the arithmetic mean was made. To compare the values in the groups, the Student's t-test was used. For the confidence level, the probability of a difference of 95% was accepted ($p < 0.05$). To compare independent groups by qualitative characteristics, the Pearson's chi-squared test χ^2 was used.

Results

According to WHO recommendations, the normal content of magnesium in serum is:

Table 1

The distribution of patients by group, sex and age

Groups	N	Clinical case (CEAP)	Age, years ($M \pm \sigma$)	Disease duration, ($M \pm \sigma$)	Sex (abs. /%)	
					Males	Females
I.	32	C2-C3 – 18 patient (56.25%) C4 – 6 patient (18.75%) C5-C6 – 8 patient (25%)	41.1 \pm 7.2	10.1 \pm 3.2	13 (40.6%)	19 (59.4%)
II.	32	C2-C3 – 18 patient (56.25%) C4 – 6 patient (18.75%) C5-C6 – 8 patient (25%)	45.2 \pm 9.3	11.1 \pm 2.7	14 (43.8%)	18 (56.2%)
III.	30	C2-C3 – 18 patient (60%) C4 – 5 patient (16.7%) C5-C6 – 7 patient (23.3%)	48.7 \pm 8.7	7.6 \pm 1.5	13 (43.3%)	17 (56.7%)
IV.	30	C2-C3 – 18 patient (60%) C4 – 5 patient (16.7%) C5-C6 – 7 patient (23.3%)	43.1 \pm 9.4	7.2 \pm 4.3	12 (40%)	18 (60%)
V.	20	—	44.1 \pm 6.2	—	8 (40%)	12 (60%)

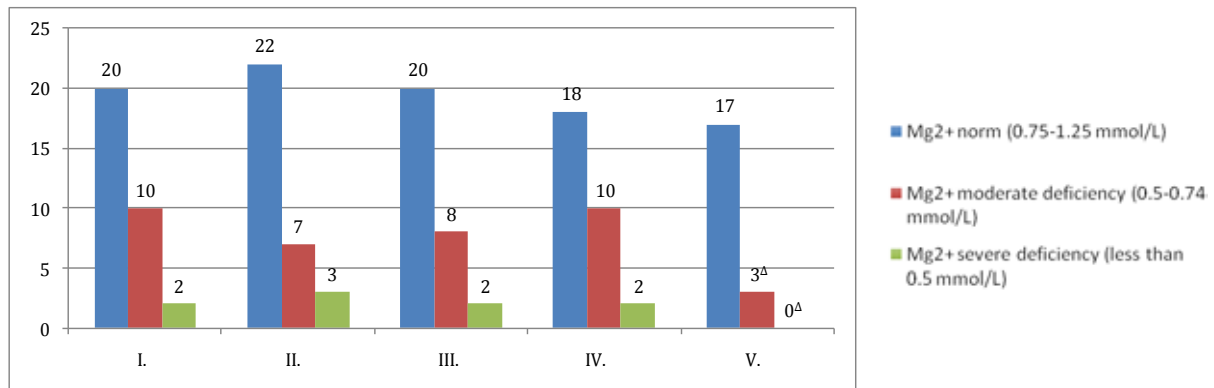


Fig. 1. Distribution of patients with magnesium deficiency in groups.

^Δ – significant difference from groups of patients with varicose veins at the stage of screening ($p < 0.05$).

- from 0.74 to 1.15 mmol/L for children,
- from 0.75 to 1.26 mmol/L for adults,
- from 0.8 to 1.05 mmol/L for pregnant women.

At the same time, 0.5-0.74 mmol/L testifies to moderate magnesium deficiency in the body, and a level below 0.5 mmol/L – to a pronounced deficiency of magnesium ions.

Blood samples of patients with varicose veins and patients of the control group were taken as initial biochemical indices. The following results were obtained. In patients with varicose veins before the start of treatment in 64.5% of cases (80 people) normal values of Mg^{2+} were observed. In

35 people (28.2%) there was a moderate decrease in magnesium concentration. And a pronounced deficit was observed in the remaining 9 patients (7.3%). In the control group, only three people had a deficiency of magnesium (15%) (Fig. 1).

Further, against the background of the therapy, a significant decrease in the number of patients with magnesium deficiency in the second and fourth groups after 1 month of therapy was registered ($p < 0.05$), and this indicator remained low throughout the study. While in the first and third groups throughout the study, the number of patients with magnesium deficiency remained at the initial level (Table 2).

Table 2

Dynamics of changes in the number of patients with magnesium deficiency

Groups	Number of patients with magnesium deficiency ($Mg^{2+} < 0.75$ mmol/L)			
	V0	V1 (after 1 month)	V2 (after 3 months)	V3 (after 6 months)
I.	37.5% (12 people)	34.4% (11 people)	34.4% (11 people)	34.4% (11 people)
II.	31.3% (10 people)	9.4%* (3 people)	3.1%* (1 person)	3.1%* (1 person)
III.	33.3% (10 people)	33.3% (10 people)	33.3% (10 people)	36.7% (11 people)
IV.	40% (12 people)	10 %* (3 people)	0%* (0 people)	3.3 %* (1 person)
V.	15% ^Δ (3 people)	–	–	–

Note: * – significant difference from the initial level ($p < 0.05$). ^Δ – Significant difference from groups of patients with varicose veins at the stage of screening ($p < 0.05$).

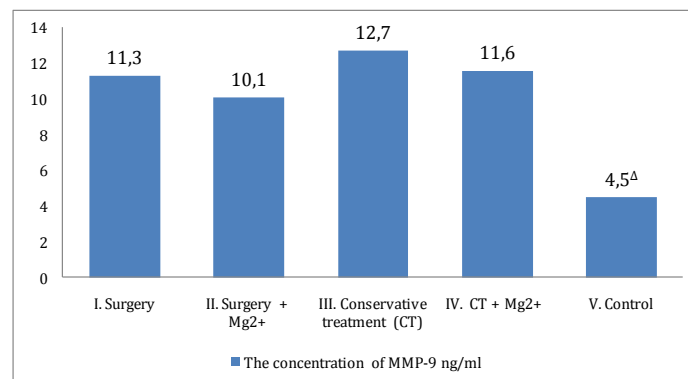


Fig. 2. The concentration of MMP-9 in patients with varicose veins and the control group at the stage of inclusion in the study.

^Δ – significant difference from groups of patients with varicose veins at the stage of screening ($p < 0.05$).

Table 3

The concentration of MMP-9 in patients of different groups (M±m)				
Groups	V0 ng/ml	V1 (after 1 month) ng/ml	V2 (after 3 months) ng/ml	V3 (after 6 months) ng/ml
I.	11.3±1.7	12.2±2.2**	11.5±1.4**	11.2±1.9**
II.	10.1±1.3	6.2±0.8*	5.4±2.1*	5.5±2.1*
III.	12.7±2.5	12.2±1.3**	11.7±2.2**	11.4±2.4**
IV.	11.6±2.1	8.7±1.1*	8.0±1.4*	7.6±0.9*
V.	4.5±1.3	—	—	—

Note: * — significant difference from the initial level ($p < 0.05$). ** — the differences are insignificant compared to the initial level ($p > 0.05$). ^Δ — Significant difference from groups of patients with varicose veins at the stage of screening ($p < 0.05$).

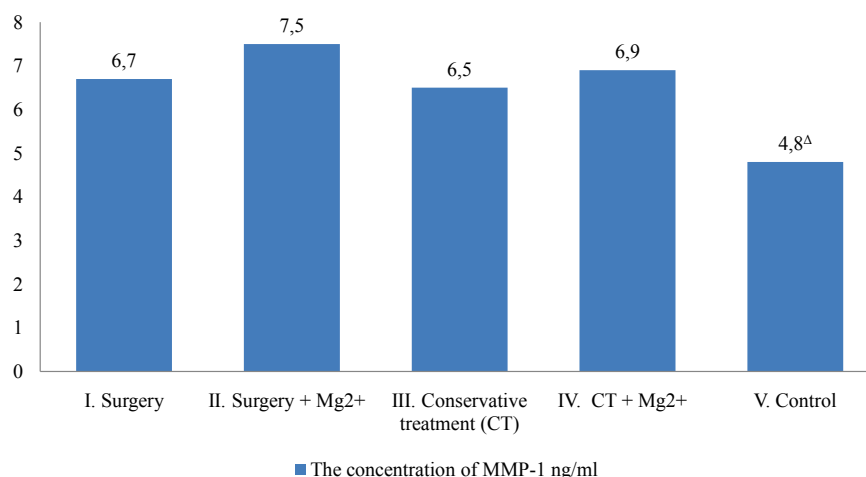


Fig. 3. The concentration of MMP-1 in patients with varicose veins and the control group at the stage of inclusion in the study.

^Δ — significant difference from groups of patients with varicose veins at the stage of screening ($p < 0.05$).

In the control group, the concentration of MMP-9 was 4.5 ± 1.32 ng/ml. In groups of patients with varicose veins, a significantly lower MMP-9 level was found in comparison with the control group (11.3 ± 4.86 ng/ml, $p < 0.05$) (Fig. 2).

One month later, the concentration of MMP-9 in the first group was 12.2 ± 2.2 ng/ml, which was statistically significantly different from the baseline. The same value was noted in patients of the third group. In the second and fourth group, the indices were 6.2 ± 0.8 ng/ml and 8.7 ± 1.1 ng/ml, which was a significant decrease compared to the initial level of MMP-9 in these groups ($p < 0.05$).

Three months later, there was a tendency to decrease MMP-9 concentration in the second and fourth groups (5.4 ± 2.1 ng/ml and 8.0 ± 1.4 ng/ml, respectively). In the first and third groups, the MMP-9 index was kept at the initial level. In the I and III groups, MMP-9 indices did not differ significantly during the entire 6-month study period (Table 3).

In the control group, the concentration of MMP-1 was 4.8 ± 0.73 ng/ml. In groups of patients with varicose veins, a significantly higher MMP-1 level was found in comparison with the control group (6.9 ± 1.16 ng/ml, $p < 0.05$) (Fig. 3).

A month later, all groups showed a tendency to

decrease in MMP-1 concentration in comparison with the initial level ($p < 0.05$). The MMP-1 index in the first group was 5.4 ± 0.5 ng/ml, in the second — 6.1 ± 0.4 ng/ml, in the third — 5.7 ± 0.3 ng/ml, in the fourth — 5.8 ± 0.6 ng/ml. Three months later, the trend towards a decrease in MMP-1 concentration in all four groups remained. Six months later, MMP-1 in all groups did not significantly differ statistically from the results that we received at the stage of patient inclusion (Table 4).

In patients with varicose veins, a higher level of TIMP-1 was observed than in the control group (210.8 ± 21.1 ng/ml and 154.4 ± 14.4 ng/ml, respectively, $p < 0.05$) (Fig. 4).

After one month of observation, the concentration of TIMP-1 in the first group was 216.5 ± 12.4 ng/ml, in the third — 212.3 ± 13.2 ng/ml, which statistically significantly did not differ from the initial index. While in the second and fourth group the indices were 274.3 ± 18.9 ng/ml and 280.5 ± 14.3 ng/ml, which was a significant increase in comparison with the initial level of TIMP-1 in these groups ($p < 0.05$).

Three months later, there was a tendency for an increase in the concentration of TIMP-1 in the second and fourth groups (285.5 ± 13.2 ng/ml and 288.1 ± 12.9 ng/ml, respectively). In the I and III

Table 4

The concentration of MMP-1 in patients of different groups (M±m)				
Groups	V0 ng/ml	V1 (after 1 month) ng/ml	V2 (after 3 months) ng/ml	V3 (after 6 months) ng/ml
I.	6.7±0.4	5.4±0.5*	5.2±0.8*	6.3±0.9**
II.	7.5±0.7	6.1±0.4*	6.2±0.5*	7.0±0.7**
III.	6.5±0.5	5.7±0.3*	5.3±0.5*	6.2±0.4**
IV.	6.9±0.4	5.8±0.6*	5.9±0.4*	6.4±0.5**
V.	4.8±1.3	—	—	—

Note: * — significant difference from the initial level ($p < 0.05$). ** — the differences are insignificant compared to the initial level ($p > 0.05$). ^Δ — Significant difference from groups of patients with varicose veins ($p < 0.05$).

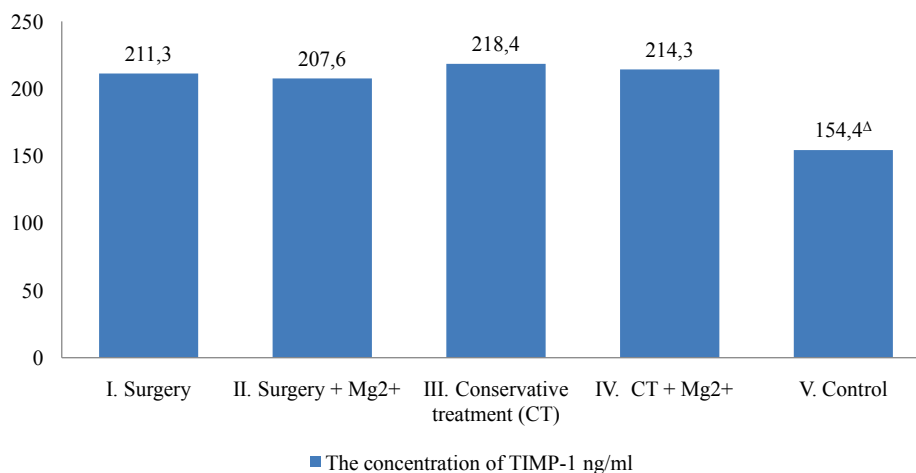


Fig. 4. The concentration of TIMP-1 in patients with varicose veins and the control group at the stage of inclusion in the study.

^Δ — significant difference from groups of patients with varicose veins at the stage of screening ($p < 0.05$)

groups, TIMP-1 values did not differ significantly throughout the 6-month study period (Table 5).

Discussion

For the first time, a complex biochemical evaluation of magnesium ions, matrix metalloproteinases, and tissue inhibitor of matrix metalloproteinases was carried out in patients with varicose disease of the lower limbs. The analysis of magnesium preparations effect in the treatment of this pathology was also performed.

In patients with varicose veins, a significantly lower magnesium level was observed compared to conditionally healthy volunteers who did not suffer from varicose veins (patients with a magnesium

deficiency of 35.5% and 15%, respectively, $p < 0.05$), indicating the presence of connective tissue dysplasia (DCT) in patients with varicose veins.

Against the background of additional therapy with magnesium drugs (magnesium orotate), there was a decrease in the number of patients with magnesium deficiency in groups of patients with varicose veins, which created favorable prerequisites for the further course of the disease from the position of connective tissue dysplasia.

There was also a significant ($p < 0.05$) decrease in MMP-9 activity in patients of Group II and Group IV after 1 month of therapy, and it was reduced during 6 months. The concentration of TIMP-1 in these groups increased on the contrary and remained elevated against the background of magnesium

Table 5

The concentration of TIMP-1 in patients of different groups (M±m)				
Groups	V0 ng/ml	V1 (after 1 month) ng/ml	V2 (after 3 months) ng/ml	V3 (after 6 months) ng/ml
I.	211.3±11.5	216.5±12.4**	207.2±10.3**	208.3±11.2**
II.	207.6±9.4	274.3±18.9*	285.5±13.2*	291.2±11.3*
III.	218.4±21.4	212.3±13.2**	205.4±9.5**	215.6±14.5**
IV.	214.3±7.7	280.5±14.3*	288.1±12.9*	275.2±11.9*
V.	154.4±14.4	—	—	—

Note: * — significant difference from the initial level ($p < 0.05$). ** — the differences are insignificant compared to the initial level ($p > 0.05$). ^Δ — significant difference from groups of patients with varicose veins at the stage of screening ($p < 0.05$).

therapy. In the 1st and 3rd groups, the differences in MMP-9 and TIMP-1 concentrations were not observed during the follow-up period in comparison with the initial index. Taking into consideration the intake of magnesium drugs in the second and fourth groups of patients, one can judge about the influence of magnesium ions on the decrease of MMP-9 activity, thereby inhibiting the extracellular matrix degradation and collagen destruction processes. The most pronounced decrease was noted in the second group, where the patients were treated surgically in addition to conservative therapy.

There is a significant ($p < 0.05$) decrease in MMP-1 activity in patients with varicose veins after 1 and 3 months of the therapy. Taking into account the intake of magnesium drugs in the second and fourth groups of patients, it can be judged that magnesium ions did not affect the activity of MMP-1, and the decrease in the indices is likely due to the effect of standard therapy for patients with varicose veins.

Conclusions

One has revealed the elevated levels of MMP-1, MMP-9 and TIMP-1 in the blood and a decrease in magnesium concentration in patients with varicose veins of the lower extremities in comparison with the control group, people without varicose veins.

There is a decrease in MMP-1 concentration during varicose veins treatment during 3 months of active therapy, both in operative and in conservative treatment groups, this indicator comes to the baseline level after 6 months.

Magnesium drugs reduce the activity of MMP-9 and increase the concentration of TIMP-1, thereby affecting the balance of MMP / TIMP in patients with varicose veins of the lower extremities.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

The study was approved by the Ethics Committee of Ryazan State Medical University named after Academician I.P. Pavlov.

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